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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,112	12/15/2003	Jeffrey S. Ross	M2051-700410	5668

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

NOTIFICATION DATE	DELIVERY MODE
01/22/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@ll-a.com
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Office Action Summary	Application No.	Applicant(s)	
	10/736,112	ROSS, JEFFREY S.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,10-16,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 8, 10-16, 33-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/16/08 has been entered.

Applicant cancels claims 3-7, 9.

Accordingly, claims 1, 8, 10-16, 33-34 are examined in the instant application.

Sequence rule

It is noted that this application is in compliance with the sequence rule (CRF entered on 12/11/08) in view of the sequence listing and the amendment of the specification of 11/25/08. The Notice to Comply with sequence rule of 12/04/08 was in cross-mail with the response of 11/25/08.

Withdrawn Rejection

The following rejection has been withdrawn in view of the amendment: 1) 112, first paragraph, written description, concerning variant PSMA, and enablement, concerning essential material, and 2) 102 rejection.

Claim Rejections - 35 USC § 112, Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, 10-16, 33-34 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons already of record in paper of 04/28/08.

The response asserts that the reference standard is PSMA expression levels in a primary tumor of a subject diagnosed with prostate cancer that does not have recurrence.

The response has been considered but is not found to be persuasive for the following reasons:

Claim 1 does not recite that the reference standard is PSMA expression levels in a primary tumor of a subject diagnosed with prostate cancer that does not have recurrence. As written, it is not clear what constitutes a reference standard, which could be anything, and is not even necessary PSMA.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8, 10-16, 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Claims 1, 8, 10-16, 33-34 remaine rejected under 35 U.S.C. 112, first paragraph, for lack of enablement for a method for determining if a subject is **at risk of prostate cancer recurrence,** for reasons already of record in paper of 04/28/08.

The response asserts that in view of the overwhelming evidence to support Applicants' finding, in contrast to Bostwick et al, 1998, the only one ten year old reference cited by the Office, which teach that PMSA level in primary prostate cancer is not predictive of prostate cancer recurrence, there is sufficient guidance provided in the present application to enable to claimed invention. The response asserts that Beckett et al, 1999, and Thomas, 2002, do not use PMSA in primary prostate cancer, but only teach that PMSA level in serum of patients having prostate cancer is not predictive of prostate cancer recurrence.

The response asserts that on the contrary, Perner et al, 2007, performed univariate and multivariate analysis of PSMA expression levels on biopsy samples from patients diagnosed with prostate cancer. The response asserts that this study evaluated biopsy samples from the primary tumor of 450 patients with prostate cancer. The response asserts that consistent with the data provided in the present application, Perner et al report that "high PSMA levels were associated with significant increase in PSA recurrence. The response submits a press release in 2006 by Cytogen, supporting Applicant's finding that PSMA expression levels in primary prostate tumor sample predict prostate cancer recurrence.

The response asserts that Tockman et al and Vandesomepele et al teach the requirement for validation of predictive markers for early detection of primary cancers and not for recurrence

in a patient population diagnosed with a cancer. The response asserts that Tockman et al. were deriving their data from a patient population, i.e., patients having breast cancer, different than the patient population in which the marker was going to be used, i.e., patients not yet diagnosed with clinical cancer. The response asserts that, however, Applicants' data was derived from the same patient population as that in which the marker will be used, namely patients diagnosed with prostate cancer.

The response has been considered but is not found to be persuasive for the following reasons:

One cannot predict that the level of PSMA in prostate cancer patients is predictive of prostate cancer recurrence, and validation of the claimed method in a tested population is necessary for the following reasons:

A) The teaching in the art is **contradictory** concerning whether PSMA level is predictive of recurrence of prostate cancer. Although the reference by Bostwick et al is 10 years old, the response does not have any objective evidence showing why the teaching of Bostwick et al is not valid. Bostwick et al, 1998, of record, also using statistical analysis, studying 184 cases with a minimum patient follow-up period of 4.5 years after treatment (p. 2256, p.2257, second column, first paragraph, p.2258, first column, third paragraph), teach that PSMA level in primary prostate cancer is not predictive of recurrence of prostate cancer. Further, the teaching of Bostwick et al is reinforced by the teaching of Beckett et al, 1999, and Thomas et al, 2002, all of record, that the level of serum PSMA in prostate cancer patient is not a predictor of prostate cancer recurrence. Although Beckett et al and Thomas et al use PSMA in the serum of prostate cancer patient, serum PSMA level reflects the severity of the disease, and thus the level of PSMA in primary

prostate cancer tissue. On the other hand, Rosenthal et al, 2001, and Murphy et al, 1998, teach that PSMA level in prostate cancer tissue, and serum of prostate cancer patient, respectively, is predictive of recurrence of prostate cancer.

B) In a similar situation with the marker hsp27 as predictive of breast cancer, where there are contradicting results, even with univariate analysis, Oesterrich et al, of record, confirm the need to perform validation studies (p.1205, first column, para before last), in view that false positive correlation does occur. This false positive correlation is also confirmed in another presumably prognosis maker, Id2, taught by Vandersompele et al, of record. This need for validation of the data is also taught by Tockman et al, of record. The teaching of Tockman et al applies as well to the instant application, especially in view of contradictory results in the art, concerning the predictive value of PSMA. Similar to the unknown population of patients not yet diagnosed with breast cancer to be tested and validated, as taught by Tockman et al, the instant claims also encompass PSMA predictive value for a population not previously tested by the instant application, i.e. any prostate cancer population, including those with low grade prostate cancer.

C) Further, the claims also encompass PSMA predictive value for **any prostate cancer population, including those with low grade prostate cancer**. The specification only disclose PSMA data for those with a mean value of Gleason score of 6.33, and statistical analysis to arrive at the predictive value (p.33). It is well known in the art that the severity of prostate cancer is correlated with Gleason scores, from 2 to 10, wherein a score of 10 is the most advanced prostate cancer (Perner et al, 2007, Human Pathol, 38: 696-701, recited by Applicant, especially table 3 on page 699). Bostwick et al, however, teach that those having Gleason scores of 3, 4 and

5 do not have recurrence within the minimum patient follow- up period of 4.5 years (p.2257, second column, first paragraph).

Further, concerning Perner et al and Cytogen, 2006, Perner et al do not have any follow-up studies after therapy to determine the number of actual recurrence. They only use statistical analysis to obtain prediction value from data of patients at the time of therapy. Further, Perner et al further teach that stratified according to Gleason score, PSMA expression is not an independent predictor of PSA recurrence (p.699, second column, last two lines, bridging p.700).

Moreover, similar to the instant application, Cytogen teaches that high PMSA level is associated with increase in prostate cancer recurrence, but only uses multivariate statistical analysis to predict disease recurrence (p.1, third paragraph). There is no confirmation of such prediction, for example, confirming recurrence from on an unknown population of prostate cancer patients that have high level of PMSA in primary prostate cancer tissue. Such confirmation, however, is necessary, in view of: 1) the teaching of Tockman et al, Vandersompele et al, and Oesterrich et al, all of record, and 2) contradictory data in the art, supra. Further, the prediction of disease recurrence taught by Cytogen, 2006 is only significant after adjusting for Gleason score and seminal vesical invasion (Cytogen report, lst three lines of third paragraph). Such limitation is not found in the claims.

In addition, one would not know how to perform the claimed method, because one cannot predict which actual level of PMSA is the value for the claimed **reference standard**, in view of the following disclosure in the specification (p.13, second paragraph):" In another aspect, the invention features a method of constructing a reference standard that includes: including data from a database described herein in the standard. For example, one can take values from a

database, perform a mathematical operation on them and use the result as a reference in arriving at a reference standard, e.g., taking an average of a plurality of values selected from the database and use the average as the standard". Further, although the specification on page 23, second paragraph discloses that term "reference standard" as used herein can refer to a standard that is a statistically significant level of PSMA expression which distinguishes subjects having recurrence and subjects that do not have recurrence, there is no data showing the level of PMSA subjects that do not have recurrence. The specification does not have any data or objective evidence that there exists a significant difference between the level of PMSA between subjects having recurrence and subjects that do not have recurrence. Not only one cannot determine what level of PMSA is the claimed reference standard, one cannot predict whether there exist a significant difference in the level of PMSA between subjects having recurrence and subjects that do not have recurrence, in view that the level of a protein in a particular type of cancer patient is unpredictable.

2. Claims 1, 8, 10-16, 33-34 also remain rejected under 35 U.S.C. 112, first paragraph, because it is not clear **which of the claimed PSMA amino acid sequence, SEQ ID NO:1 or SEQ ID NO:2** is the wild type and which one is the variant thereof**.** One cannot predict the level of which of SEQ ID NO:1 and SEQ ID NO: 2 is increased, wherein said increase is statistically significant between subjects having prostate cancer recurrence and those diagnosed with prostate cancer, that do not have recurrence. It is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type, in view of the teaching of Schmid et al, Conner et al, all of record.

New Rejection Due to the Amendment

Specification

The amendment of the specification of 05/16/08 is objected to for the following reasons:

The amendment deletes references originally cited on page 17 of the specification.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 4, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643